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CURARE-LIKE ACTIVITY OF MONO-QUATERNARY SALTS CONTAINING ADAMANTYL RESIDUE AT THE NITROGEN ATOM

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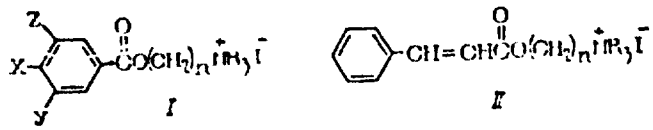
Substitution of N-methyl residue for N-adamantyl changes the mechanism of action of derivatives of benzoic and cinnamic acids. Adamantyl analogs of trimethylammonium compounds induced flaccid paralysis characteristic of nondepolarizing blockage.

As shown in previous works, mono-quaternary salts of alkamine esters of benzoic and cinnamic acids types (I) and (II) exhibit a pronounced curare like action /1/.



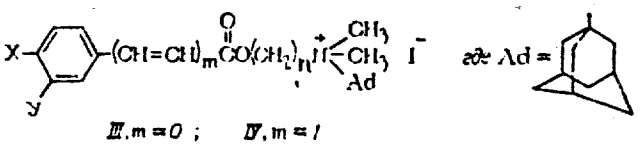
I II

By activity, some of these compounds can be compared with the most effective muscle relaxants pertaining to the group of bis-quaternary ammonium salts. Like the majority of mono-quaternary salts, they act extremely transitory. The latter, apparently, is related largely with the presence of ester bond hydrolyzed in the organism. It should be attributed to the deficiencies of compounds (I) and (II) hampering their possible use in anaesthesiologic practice that they induce a depolarising neuromuscular block. As is known, the antidepolarizing muscle relaxants /2/ whose action can be regulated by the application of antagonists (for example, proserine) are the most interesting for application in surgery. They do not destroy the distribution of potassium ions and do not cause a series of side effects typical for depolarizing preparations.

Earlier attempts were repeatedly made by various sorts of structural changes to transform depolarizing muscle relaxants into practically more valuable antidepolarizing compounds. The potentiality of such a change for mono-quaternary muscle relaxants is already noted in principle. Thus it is shown that for salts of tetramethylammonium, a sequence substitution of one of the methyl groups by an alkyl residue with a constantly increasing chain length means that when the number of carbon atoms in the chain is greater than 12, the substance loses depolarizing properties and begins to act like a non-depolarizing type/3/. On the basis of this data, compounds were studied in whose onium center is introduced in a high degree a lipophilic and voluminous residue. It could have been expected that in so doing, the distribution of substances, the ease of the muscle relaxant molecules approach to corresponding

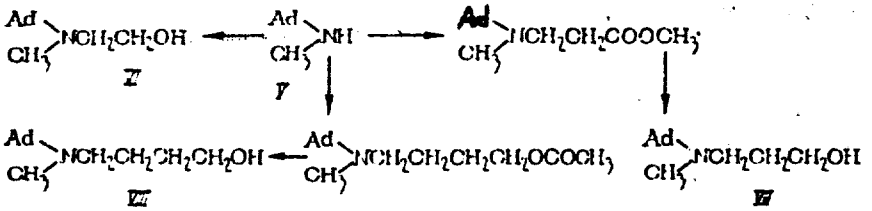
receptors, and the strength of the bonds between them, would be essentially changed. There is data that depolarizing and non-depolarizing curare like agents are unevenly fixed in the region of the skeletal muscles' terminal plates /4,5/, in whose synaptic membranes' structure the lipophilic formations occupy an important place /6/. It is also known that the introduction of adamantyl groups in the structures of antidiabetic compounds /7/, hormonal preparations /8/, and other physiologically active substances /9/ causes interesting changes in the character of these compounds activity.

A series of methiodides of alkamine esters of benzoic (III) and cinnamic (IV) acids were synthesized, analogous by structure to salts I and II, but containing at the quaternary nitrogen atom a 1-adamantyl residue instead of a methyl group.



III. m = 0 ; IV. m = 1

As 1-bromadamante usually does not form a quaternary salt with tertiary amines, it was necessary to obtain, starting from 1-(N-methylamino) adamantane (V) /10/ a series of amino alcohols with an adamantyl residue at the nitrogen atom.



β-/N-methyl-N-(1-adamantyl) amino/ethanol (VI) is synthesized by the action of ethylene oxide on V. By addition of an equimolecular quantity of V to a methyl ester of acrylic acid, a methyl ester of β-/N-methyl-N-(1-adamantyl)amino/propionic acid is obtained, reduced further by 2 moles of lithium alumohydride to γ-/N-methyl-N-(1-adamantyl)amino/propanol (VII). By a reaction of 2 moles of V with δ-bromabutylacetate, δ-/N-methyl-N-(1-adamantyl) amino/butyl acetate is obtained, which without isolation in an individual state is hydrolized to δ-/N-methyl-N-(1-adamantyl)amino/butanol (VIII). Amino alcohol VI is a crystal substance; amino alcohols VII and VIII are viscous liquids, distilling without decomposition in a high vacuum and characterized as hydrochlorides and methiodides (Table 1).

The transformation of the obtained amino alcohols (VI-VII) into complex esters of benzoic or substituted benzoic acids is accomplished by their interaction with an equimolecular quantity of

corresponding acid chloride (Standard experiment A). The basic cinnamic acid esters are derived by re-esterification from methyl esters of cinnamic acids and amino alcohols in the presence of alcoholate (Standard experiment B). In both variants the seperation of the forming alkamine ester from the amino alcohols not reacting is conducted by fractional alkalization of a solution of reaction mixture in acid; in addition, in the majority of cases even without distillation the precipitated esters showed completely satisfactory analysis results. The extraction of methiodides was conducted by heating a solution of reagents in acetone. The results of the analysis and the constants of the synthesized compounds are presented in Table 2.

During pharmacological studies of compounds (III) and (IV), their curare like action was compared with the action of analogously structured compounds (I) and (II). It is shown that the substitution of an N-methyl residue by an N-adamantyl causes a change of the substance's mechanism of action, this applying both to the benzoic acid derivatives (I) and (III) and to the cinnamic acid derivatives (II) and (IV). In all cases, trimethylammonium compounds induce a spastic paralysis in chicks typical for depolarizing agents, at t the same time that their adamantyl analogs induced a flaccid paralysis characteristic for a nondepolarzing block (see Table 2). A change of the compounds' mechanism of action during introduction of adamantyl residue into a cationic group is accompanied by a sharp decline of curare like activity (according to the data of experiments on cats, by 200-300 times).

If a value n is compared, then for the tested adamantyl derivatives (unlike trimethylammonium) the number of methylene groups in the amino alcohol part of the molecule does not play an essential role. When n= 2, 3, or 4, the activity of mono-quaternary ammonium salts or alkamine esters of benzoic and cinnamic acids are of the same order. Introduction into the aromatic ring of a nitrogroup or methoxygroups also changes activity little.

For a much wider study of the found dependencies, it was of interest to see what influence the presence of an adamantyl residue exhibits on the mechanism of action of other cholinomimetics which are mono-quaternary ammonium salts, primarily tetramethylammonium iodide (Xa) and acetyl choline (XIa). The synthesis of an adamantyl analog of IX (IXb) is derived by heating VI with methyl iodide (see above); its treatment with acetic anhydride results in an adamantyl analog of acetylcholine (XIb).

The results of the pharmacological tests of the compounds (IX-XI) showed that in these cases the substitution of a methyl residue by an adamantyl is accompanied by the transformation of a depolarizing substance into a nondepolarizing one, their activity declining simultaneously (Table 3). The observed change of the mechanism

of action can be associated with a significant amount of adamantyl residue. However it could sooner be proposed that its high lipophylness plays a basic role, essentially changing both the potentiality of the substance's penetration through hydrophylic and hydrophobic structures of subsynaptic membranes and the conditions of its interaction with cholinoreceptors.

Experimental part.

The yields and constants of the extracted compounds and their derivatives are presented in Tables 1 and 2.

β-/N-methyl-N-(1-adamantyl)amino/ethanol (VI). To a solution of 15 g. V in 70 ml. of methanol is added a solution of 20 g. ethylene oxide in 30 ml. methanol by dripping at 20°. The temperature of the reaction mixture in the course of an hour is brought up to 40°, during the next hour to 55° , maintained at this temperature for half an hour, after which the methanol and excess ethylene oxide are distilled off in a vacuum. The crystal residue is dissolved in 120 ml. of absolute ester and filtered with coal. After evaporation of the ester, 15.1 g. of crystals, m.p. 56-58°, are obtained.

Hydrochloride. Obtained by acidification of a solution of 2 g. VI in 10 ml. of ester with an ester solution of hydrogen chloride until a congo blue coloration. Yield: 2.1 g. (85.7%).

Methiodide. Extracted by heating a solution of 2.5 g. VI and 2.2 ml. methyl iodide until the disappearance of the alkaline reaction of the mixture (which requires about 3 hours). Yield: 3.75 g. (81%).

γ-/N-methyl-N-(1-adamantyl)amino propanol (VII). To a solution of 3.52 g. of V in 6 ml. of methanol at a temperature not higher than 40° is added by dripping 1.8 g. of methyl ester of acrylic acid in 4 ml. of methanol; the mixture is left to stand several days at room temperature. After evaporation of the methanol in a vacuum, there remains in the form of a thick oil methyl ester of β-/N-methyl-N-(1-adamantyl)amino/propionic acid. Yield: 4.86 g. (92.2%). Found, %: C 71.52, 71.83; H 10.00, 10.03; N 5.61, 5.72; $C_{15}H_{25}NO$. Calculated, %: C 71.67; H, 10.02; N 5.57.

Hydrochloride, m.p. 151-153°. Found, %: C 62.54, 62.61; H 9.00, 8.90; Cl' 12.57, 12.61. $C_{15}H_{25}NO \cdot HCl$. Calculated, %: C 62.53; H 9.02; Cl' 12.33.

The obtained ester is dissolved in a diethyl ester, 1.52 g. of lithium alumohydride added, and the reactive mixture heated for 8 hours. Then 3 ml. of water and 9 ml. of tetrahydrofurane are poured in during cooling, the mixture boiled another 30 min, the residue filtered off, and after distillation of the solvents in a

vacuum, 3.45 g. (81%) of VI in the II form of a colorless oil is obtained.

δ - N-methyl-N-(1-adamantyl)amino/butanol (VIII). A solution of 2.65 g. δ-bromobutylacetate /11/ and 4.46 g. of V in 40 ml. of toluene is heated at boiling and agitated for 15 hours. The precipitated residue of hydrobromide of V is filtered off, the toluene distilled off from the filtrate in a vacuum, the remaining oil triturated with 5 ml. of water, a 40% solution of hydrobromide acid added until a congo blue coloration, and the mixture heated at boiling for 3 hours, the oil being almost totally transformed into a solution. The solution is extracted by ester, the ester layer discarded and the aqueous layer after treatment with oil is alkalinized with a 40% solution of caustic sodium and saturated with potash. The precipitated oil is extracted by ester, the ester solution dried, and after distillation of the solvent, a liquid base of amino alcohol is obtained.

δ-/N-methyl-N-(1-adamantyl)amino/butyl benzoate acid (Standard experiment A). To a solution of 0.5 g. VIII in 20 ml. of dry dichloroethane at a temperature of 0-20° is added 0.3 g. of benzoyl chloride and the mixture left to stand 16 hours at room temperature, after which the dichloroethane is distilled off and the residue in 5 ml. of water. The solution is extracted by ester, the ester layer discarded, the aqueous layer filtered with coal and alkalinated by an ammonium solution, the precipitated oil extracted by ester. After drying out the extract with magnesium sulfate and evaporating the ester an alkanine ester base is obtained as a viscous oil. Yield: 0.6 g. The hydrochloride is obtained in an ester solution, the methiodide in an acetone solution.

γ-/N-methyl-N(1-adamantyl)amino/propyl ester of 3, 4-diethoxy-cinnamic acid (Standard experiment B). To 2.8 g. VII is added a grain of metallic sodium and the mixture gradually heated to 80° for 40 min, passing dry nitrogen through it. Then 1.08 g. of methyl ester of 3, 4-diethoxycinnamic acid is added and, continuing to pass nitrogen through it, the mixture is maintained at a residual pressure of 110-115 mm for 2 hours at a temperature of 80-85° and 2 hours at 100°. Then it is treated with 2 n. by a solution of hydrochloric acid until a congo violet coloration, extracted by ester, the extract dried, and after distillation of the solvent, 1.1 g. (61.8%) of amino acid in the form of a thick oil is obtained.

Methiodide of β-/N-methyl-N-(1-adamantyl)amino/ethyl acetate (XIb). A mixture of 2.1 g. of methiodide VI and 2. g. of acetic anhydride is heated at 140° for 30 min. The obtained melt during cooling is crystallized. It is washed with ester and recrystallized from alcohol. Yield: 1.5 g. (65.2%), m.p. 188-190°. Found, %: C 49.20, 49.22; H 7.35, 7.51; I' 32.60, 32.76. $C_{16}H_{28}INO_2$. Calculated %: C 48.85; H 7.17; I' 32.27.

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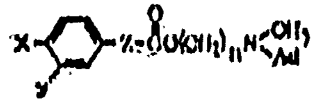
Table 1

ω-N-Methyl-N-(1-adamantyl)amino/alkanols

Compound	Gen. Yield (%)	Base: found (in %) C	H	N	Gross wgt. formula	Base: calculated (%) C	H	N	Hydrochloride: melt. pt. (deg)	Cl' found %	Cl' calculated %	Methiodide: melt pt. (deg)	I' found %	I' calculated %
VI	80,2	74,52 74,58	11,16 11,03	7,03 6,92	$C_{13}H_{23}NO$	74,59	11,07	6,69	207—9	14,14 14,08	14,42	205—206	36,30 36,16	36,13
VII	71,7	75,64 75,55	11,41 11,36	6,46 6,53	$C_{14}H_{25}NO$	75,28	11,28	6,27	189—91	13,41 13,34	13,64	193—195	35,23 35,24	37,74
VIII	76,3	76,06 76,14	11,60 11,39	5,75 5,91	$C_{15}H_{27}NO$	75,89	11,46	5,90	167—9	12,63 12,72	12,94	120—122	33,14 32,62	33,37

Basic ethers of benzoic and cinnamic acids and their methiodides (III) and (IV)  1 Table 2.

X	Y	Z	n	Base: Yield (%)	Base: found (%) C	Base: found (%) H	Base: found (%) N	Base: Gross wgt. fmla.	Base: calculated (%) C	Base: calculated (%) H	Base: calculated (%) N	Methiodide: M. p.	Methiodide: I fpd %	Methiodide: I calc %	Methiodide: curare-like act.: Doses (mg/kg) intravenously	Methiodide: character of paralysis
H	H	—	2[a]	86,2	76,42 76,36	8,42 8,55	4,51 4,58	$C_{18}H_{17}NO_2$	76,03	8,68	4,46	193—5	28,08 28,22	27,87		flaccid, 6-8.
H	H	—	3[b]	78,1	77,24 77,31	8,95 9,10	4,35 4,55	$C_{19}H_{19}NO_2$	77,02	8,92	4,27	220—2	26,72 26,96	27,10		flaccid, 6-8
H	H	—	4	84,5	77,23 77,54	9,32 9,41	4,25 4,01	$C_{20}H_{21}NO_2$	77,37	9,15	4,09	203—5	26,47 26,63	26,35	10—12 (0,2—0,25)	flaccid, 4-5 (spastic, 0.3-0.4)
CH_3O	CH_3O	—	4[c]	72,9	71,65 71,49	8,84 8,63	3,60 3,68	$C_{22}H_{25}NO_4$	71,78	8,78	3,48	158—6	23,88 23,81	23,88		flaccid, 5-7
NO_2	H	—	4[d]	60,1	68,30 68,23	7,76 7,81	7,34 7,29	$C_{20}H_{20}N_2O_4$	68,37	7,82	7,24	202—4	24,38 24,27	24,02	12—14 (0,05—0,06)	flaccid, 4-6 (spastic, 0.15-0.2)
CH_3O	CH_3O	—CH=CH—	2	87,0	71,91 72,26	8,46 8,51	3,58 3,70	$C_{22}H_{29}NO_4$	72,15	8,32	3,50	207—9	23,76 23,62	23,44	8—9	flaccid, 5-6
CH_3O	CH_3O	—CH=CH—	3	73,6	72,40 72,56	8,60 8,77	3,60 3,72	$C_{23}H_{31}NO_4$	72,66	8,53	3,40	216—8	22,83 23,07	22,85	9—10	flaccid, 3-4
CH_3O	CH_3O	—CH=CH—	4[e]	61,8	72,59 72,82	8,72 8,86	3,59 3,34	$C_{24}H_{33}NO_4$	73,03	8,72	3,27	254—6	22,42 22,52	22,28	7—8 (0,03—0,05)	flaccid, 3-4 (spastic, 0.15-0.25)

[1]Experiments on anesthetized cat (Cloralose 60 mg/kg with urethane 400 mg/kg intravenously). Peripheral segment of sciatic nerve was irritated with supramaximal rectangular stimuluses with frequency of 1 stim/sec and duration of 0.5 msec.

[2]Hydrochloride, m.p. 217-218°, strongly dissolved in water, Found, %: Cl' 10.04, 9.99. Calculated, %: Cl' 10.10.

[3]Hydrochloride, m.p. 183-185°. Found, %: Cl' 9.52, 9.64. Calculated, %: Cl' 9.75

[4]Hydrochloride, m.p. 92-94°. Found, %: Cl' 8.17, 8.33. Calculated; %: 8.09.

[5]Base, m. p. 42-43°. Hydrochloride: m. p. 176-178°, strongly dissolved in water. Found, %: Cl' 8.02, 8.14. Calculated, %: Cl' 8.38.

[6]Hydrochloride, m.p. 112-114°. Found, %: Cl' 7.44, 7.38. Calculated, %: Cl' 7.64

Footnote: In parenthesis are cited test results of analogous compounds where Ad is substituted for CH_3.

Table 3

Effect of derivatives at nitrogen on the character of paralyzing action of mono-quaternary ammonium compounds.

Compound	Character chick paralysis in doses (mg/kg) intravenously, showing paralyzing activity [1]
$CH_3\overset{+}{N}(CH_3)_3I^-$ (IX)	Spastic
$CH_3\overset{+}{N}(CH_3)_2(Ad)I^-$ (IXa)	Flaccid, 30-40
$HOCH_2CH_2\overset{+}{N}(CH_3)_3I^-$ (X)	Spastic, 50-60
$HOCH_2CH_2\overset{+}{N}(CH_3)_2(Ad)I^-$ (Xa)	Flaccid, 40-60
$CH_3COOCH_2CH_2\overset{+}{N}(CH_3)_3Cl^-$ (XI)	Spastic, 0.10-0.15
$CH_3COOH_2CH_2\overset{+}{N}(CH_3)_2(Ad)I^-$ (XIa)	Flaccid, 40-50

[1] The unverified melting and boiling points are cited.